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(54) Title: METHOD FOR THE TREATMENT OF INSOMNIA

(57) Abstract

The instant invention is a method of using certain analogs of glutamic acid and gamma-aminobutyric acid to treat insomnia.

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METHOD FOR THE TREATMENT OF INSOMNIA

BACKGROUND OF THE INVENTION

1. Field Of The Invention

The present invention relates to the use of analogs of glutamic acid and gamma-aminobutyric acid (GABA) for the treatment of insomnia.

2. Description of Related Art

GABA analogs are known agents useful in antiseizure therapy for central nervous system disorders such as epilepsy, Huntington's chorea, cerebral ischemia, Parkinson's disease, tardive dyskinesia, and spasticity. It has also been suggested that the compounds can be used as antidepressants, anxiolytics, and antipsychotics. See WO 92/09560 (United States Serial Number 618,692 filed November 27, 1990) and WP 93/23383 (United States Serial Number 886,080 filed May 20, 1992).

WO 97/33858 teaches that compounds related to gabapentin are useful or treating epilespy, faintness attacks, hypokinesia, cranial disorders, neurodegenerative disorders, depression, anxiety, panic, pain, and neuropathological disorders. WO 97/33858 does not specify what forms of pain are treated.

Additionally, the compounds of the invention are known for treatment of neuropathic pain. For example, see Rosner H; Rubin L; Kestenbaum A., Gabapentin adjunctive therapy in neuropathic pain states. Clin J Pain, 1996 Mar, 12:1, 56-8; Segal AZ; Rordorf G., Gabapentin as a novel treatment for postherpetic neuralgia. Neurology, 1996 Apr, 46:4, 1175-6; Wetzel CH; Connelly JF., Use of gabapentin in pain management. Ann Pharmacother, 1997 Sep, 31:9, 1082-3; Zapp JJ., Postpoliomyelitis pain treated with gabapentin [letter]. Am Fam

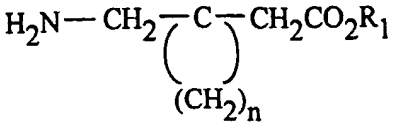
Physician, 1996 Jun, 53:8, 2442, 2445; Cheville A, et al., Neuropathic pain in radiation myelopathy:a case report. Program book, American Pain Society (14th Annual Scientific Meeting). Abstract #95823, p. A-115; Sist T; Filadora V; Miner M; Lema M., Gabapentin for idiopathic trigeminal neuralgia: report of two cases. Neurology, 1997 May, 48:5, 1467; Waldman SD, Tutorial 28: Evaluation and Treatment of Trigeminal Neuralgia. Pain Digest (1997) 7:21-24; Mellick LB; Mellick GA., Successful treatment of reflex sympathetic dystrophy with gabapentin [letter]. Am J Emerg Med, 1995 Jan, 13:1, 96; Mellick GA; Seng MI., The use of gabapentin in the treatment of reflex sympathetic dystrophy and a phobic disorder. Am J Pain Manage 1995; 5:7-9; Mellick GA; Mellicy LB; Mellick LB., Gabapentin in the management of reflex sympathetic dystrophy [letter]. J Pain Symptom Manage, 1995 May, 10:4, 265-6; Mellick GA; Mellick LB., Reflex sympathetic dystrophy treated with gabapentin. Arch Phys Med Rehabil, 1997 Jan, 78:1, 98-105 and Mackin GA., Medical and pharmacologic management of upper extremity neuropathic pain syndromes. J Hand Ther, 1997 Apr-Jun, 10:2, 96-109.

Insomnia and sleeplessness are common problems. Often, the insomnia or sleeplessness is precipitated by stress, emotional and physical causes.

U.S. Patent No. 5,510,381, directed to the use of gabapentin to treat mania, mentions one study in which gabapentin has also been found to enhance delta-wave (deep) sleep. This effect is beneficial in acute mania and also leads to reducing the risk for onset of a new episode of mania.

SUMMARY OF THE INVENTION

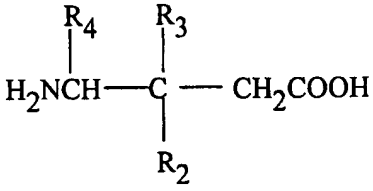
This invention provides a method for treating insomnia in a mammal comprising administering to a subject suffering from insomnia an effective amount of a GABA analog. A preferred embodiment utilizes a cyclic amino acid compound of Formula I



I

wherein R_1 is hydrogen or lower alkyl and n is an integer of from 4 to 6, and the pharmaceutically acceptable salts thereof. An especially preferred embodiment utilizes a compound of Formula I where R_1 is hydrogen and n is 4, which compound is 1-(aminomethyl)-cyclohexane acetic acid, known generically as gabapentin.

In another embodiment, the invention includes treating insomnia with a compound of Formula II.



II

wherein R_2 is a straight or branched alkyl of from 1 to 6 carbon atoms, phenyl, or cycloalkyl having from 3 to 6 carbon atoms; R_3 is hydrogen or methyl; and R_4 is hydrogen, methyl, or carboxyl; or an individual enantiomeric isomer thereof; or a pharmaceutically acceptable salt thereof, in unit dosage form, to a mammal in need of said treatment.

Preferred compounds of the invention are those wherein R_4 and R_3 are hydrogen, and R_2 is $-(CH_2)_{0-2}$-i C_4H_9 as an (R), (S), or (R,S) isomer.

The more preferred compounds of Formula II invention are (S)-3-(aminomethyl)-5-methylhexanoic acid and 3-aminomethyl-5-methyl-hexanoic acid, now known generically as pregabalin.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The method of this invention utilizes any GABA analog. A GABA analog is any compound derived from or based upon gamma-aminobutyric acid. The compounds are readily available, either commercially, or by synthetic methodology well-known to those skilled in the art of organic chemistry. The preferred GABA analogs to be utilized in the method of this invention are cyclic amino acids of Formula I. These are described in U.S. Patent 4,024,175, which is incorporated herein by reference. Another preferred method utilizes the GABA analogs of Formula II, and these are described in U.S. Patent 5,563,175 which is incorporated herein by reference.

All that is required to practice the method of this invention is to administer a GABA analog in an amount that is effective to treat insomnia. Such amounts will generally be from about 1 to about 300 mg per kg of subject body weight. Typical doses will be from about 10 to about 5000 mg per day for an adult subject of normal weight. It is expected that common doses that might be administered could be from 100 mg three times a day up to 600 mg four times a day. Commercially available capsules of 100 mg, 300 mg, and 400 mg of gabapentin can be administered. Alternate forms include liquids and film-coated tablets.

If a compound of Formula II , such as pregabalin is used, the dosage level is one sixth that of gabapentin. The dosage range for pregabalin is from about 0.15 mg to about 50 mg per kg per day of subject body weight. Typical dosages for pregabalin will be from about 1.6 mg to about 840 mg per day with individual dosages ranging from abut 0.15 mg to about 65 mg per dose.

The compounds used in the present invention may form pharmaceutically acceptable salts with both organic and inorganic acids or bases. For example, the acid addition salts of the basic compounds are prepared either by dissolving the free base in aqueous or aqueous alcohol solution or other suitable solvents containing the appropriate acid and isolating the salt by evaporating the solution.

Examples of pharmaceutically acceptable salts are hydrochlorides, hydrobromides, hydrosulfates, etc. as well as sodium, potassium, and magnesium, etc. salts.

The compounds of the Formula II can contain one or several asymmetric carbon atoms. The invention includes the individual diastereomers or enantiomers, and the mixtures thereof. The individual diastereomers or enantiomers may be prepared or isolated by methods already well-known in the art.

Pharmaceutical compositions of the compound of the present invention or its salts are produced by formulating the active compound in dosage unit form with a pharmaceutical carrier. Some examples of dosage unit forms are tablets, capsules, pills, powders, aqueous and nonaqueous oral solutions and suspensions, and parenteral solutions packaged in containers containing either one or some larger number of dosage units and capable of being subdivided into individual doses. Some examples of suitable pharmaceutical carriers, including pharmaceutical diluents, are gelatin capsules; sugars such as lactose and sucrose; starches such as corn starch and potato starch, cellulose derivatives such as sodium carboxymethyl cellulose, ethyl cellulose, methyl cellulose, and cellulose acetate phthalate; gelatin; talc; stearic acid; magnesium stearate; vegetable oils such as peanut oil, cottonseed oil, sesame oil, olive oil, corn oil, and oil of theobroma; propylene glycol, glycerin; sorbitol; polyethylene glycol; water; agar; alginic acid; isotonic saline, and phosphate buffer solutions; as well as other compatible substances normally used in pharmaceutical formulations. The compositions of the invention can also contain other components such as coloring agents, flavoring agents, and/or preservatives. These materials, if present, are usually used in relatively small amounts. The compositions can, if desired, also contain other therapeutic agents.

The percentage of the active ingredients in the foregoing compositions can be varied within wide limits, but for practical purposes it is preferably present in a concentration of at least 10% in a solid composition and at least 2% in a primary liquid composition. The most satisfactory compositions are those in which a

much higher proportion of the active ingredient is present.

Routes of administration of the subject compound or its salts are oral or parenteral. For example, a useful intravenous dose is between 5 and 50 mg and a useful oral dosage is between 20 and 800 mg. The dosage is within the dosing range used in treatment of pain or as would be with the needs of the patient as described by the physician.

The benefit of using GABA analogs to treat insomnia is that they are not addictive. Additionally, GABA analogs have a half-life in the body that is suitable to work during the evening and subsequently clear the body by morning to allow for easy arousal. GAGA analog's, particularly gabapentin's, method of action is different from other sleep enchancing agents. The GABA analogs can be combined with other agents to enhance the sleep inducing effects. Such agents include melatonin, trytophan, valerian, passiflora, antihistamines, such as diphenydramine hydrochloride or doxylamine succinate, densokiazepene and non-benzodipend hypnotics.

Additional advantages of using the compounds of Formula I and II, especially gabapentin and pregabalin, in the present invention include the relatively nontoxic nature of the compounds, the ease of preparation, the fact that the compounds are well-tolerated, and the ease of IV administration of the drugs. Gabapentin has few interactions with major classes of drugs since it is not metabolized in the liver, but rather excreted unchanged from the body. Further, the drugs are not metabolized in the body. The subjects treated with the method of the present invention are mammals, including humans.

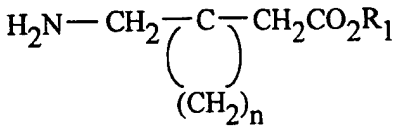
The GABA analogs used in the method of the present invention are not addictive. This is a significant advantage over other sleep aids. Also, these compounds have a half life that is suitable to work during the evening and subsequently clear the body by morning to allow for easy arousal. The method of action of the GABA analogs is different than other hypnotics and thus can be

combined with them to enhance the sleep inducing effects. These agents could include melatonin, trytophan, valerian, passiflora, classical antihistamines such as diphenhydramine hydrochloride or doxylamine succinate, as well as benzodiazepene and non-benzodiazepene hypnotics.

What is claimed is:

1. A method for treating a mammal suffering from insomnia comprising administering to said mammal a pharmaceutical composition comprising an effective amount of a GABA analog.

2. The method according to claim 1, wherein the GABA analog is the compound according to Formula I:



I

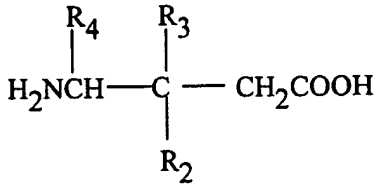
wherein R_1 is hydrogen or lower alkyl and n is an integer of from 4 to 6, and the pharmaceutically acceptable salts thereof.

3. The method according to claim 2, wherein Formula I comprises gabapentin.

4. The method according to claim 2, comprising from about 10 mg to about 400 mg of Formula I.

5. The method according to claim 3, comprising from about 10 mg to about 400 mg of gabapentin.

6. The method according to claim 1, wherein the GABA analog is a compound according to Formula II:



II

wherein R_2 is a straight or branched alkyl of from 1 to 6 carbon atoms,

phenyl, or cycloalkyl having from 3 to 6 carbon atoms; R_3 is hydrogen or methyl; and R_4 is hydrogen, methyl, or carboxyl.

7. The method according to claim 11, wherein Formula II comprises pregabalin.

8. The method according to claim 11, comprising from about .15 mg to about 65 mg of Formula II.

9. The method according to claim 12, comprising from about .15 mg to about 65 mg of pregabalin.

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(71) Applicant *(for all designated States except US)*: WARNER-LAMBERT COMPANY [US/US]; 201 Tabor Road, Morris Plains, NJ 07950 (US).

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(74) Agents: RYAN, M., Andrea; Warner-Lambert Company, 201 Tabor Road, Morris Plains, NJ 07950 (US) et al.

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(54) Title: USE OF CABA-ANALOGUES FOR TREATING INSOMNIA

(57) Abstract

The instant invention is a method of using certain analogs of glutamic acid and gamma-aminobutyric acid to treat insomnia.

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INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/US 99/15058

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/197

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 510 381 A (PANDE ATUL C) 23 April 1996 (1996-04-23) cited in the application	1-5
Y	column 2, line 21-26; claim 1; table 1	6-9
X	M.L. RAO ET AL.: "Gabapentin augments whole blood serotonin in healthy young men" FILE BIOSIS. AN=PREV1988862094727, XP002132906	1-5
Y	abstract & J. NEURAL TRANSMISSION, vol. 73, no. 2, 1988, pages 129-134,	6-9
	-/—	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 March 2000	05/04/2000

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/US 99/15058

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	F. PLACIDI ET AL.: "Effect of chronic treatment with Gabapentin on nocturnal sleep in epilepsy" AMERICAN EPILEPSY SOCIETY, ANNUAL MEETING, BOSTON, DEC. 4-7, 1997, 'Online! XP002132907 Retrieved from the Internet: <URL:http://epilepsy-international.com/meetings/abstracts/aaaaaaaf/0/643/> 'retrieved on 2000-03-10!	1-5
Y	abstract	6-9
P,X	M. KARAM-HAGE ET AL.: "Gabapentin is helpful for insomnia in alcohol-dependent patients during early recovery" ALCOHOLISM CLINICAL AND EXPERIMENTAL RESEARCH , vol. 23, no. 5, suppl., May 1999 (1999-05), page 81A XP002132908	1-5
Y	abstract	6-9
Y	FIELD M J ET AL: "GABAPENTIN (NEURONTIN) AND S-(+)-3-ISOBUTYLGABA REPRESENT A NOVEL CLASS OF SELECTIVE ANTIHYPERALGESIC AGENTS" BRITISH JOURNAL OF PHARMACOLOGY,GB,BASINGSTOKE, HANTS, vol. 121, no. 8, 1 January 1997 (1997-01-01), pages 1513-1522, XP002043785 ISSN: 0007-1188 the whole document	6-9

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 99/15058

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although all the claims are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

information on patent family members

Inter: nal Application No
PCT/US 99/15058

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5510381 A	23-04-1996	AU 702435 B	18-02-1999
		AU 5668996 A	29-11-1996
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